

D' difference in isoelectric point appears to be related to the different distribution of light and heavy subunits in each type. Specifically, heavy subunit-rich ferritin are relatively acidic, and light chain rich ferritin are relatively basic (Covell, et al., in *Ferritin and Isoferritins as Biochemical Markers*, p. 49-65, 1984, Elsevier). Current studies indicate that the H and L subunits are encoded by a complex group of genes.--

Please replace the paragraph beginning at page 2, line 13, with the following rewritten paragraph:

D² --A specific type of acidic isoferritin has been shown to be characteristic of neoplastic cells and placental cells (Drysdale and Singer, *Cancer Res.*, **34**:3352, 1974). This protein is also known as oncofetal ferritin or placental isoferritin (PLF). Human placental ferritin has been shown to be composed predominantly of a single subunit type comigrating with a liver ferritin standard on SDS-PAGE (Brown et al., *Biochem. J.*, **182**:763, 1979). However, an immunoradiometric assay performed with anti-human spleen ferritin has shown tissue specific antigenicity for PLF (Brown et al., *supra*). A three subunit structure has been revealed for PLF (Moroz et al., *G. I. Pat. Clin.*, **1**:17-23, 1986). In addition to the L and H subunits characteristic of all ferritin, there is also a high molecular weight (43 kDa) subunit which appears to be unique for human placenta, and thus provides a potential site for identification of the placental isoferritin molecule as distinguished from any other type of ferritin.--

(Please replace the paragraph beginning at the bottom of page 2, with the following rewritten paragraph:)

--Various ferritin isoforms have been isolated from normal and malignant tissues, the most acidic ones predominating in tumor and fetal tissues (Drysdale J., 1976, *Ciba Found. Symp.* **51**:41; Arosio et al., *J. Biol. Chem.*, **253**:4451, 1978). It has been suggested that the assay of acidic isoferritin in the serum

D² may be of value in the diagnosis of malignancy (Hazard et al., *Nature*, **265**:755, 1977). Elevated concentrations of serum ferritin were found in patients suffering from a variety of malignant diseases, including acute lymphocytic leukemia (ALL) (Matzner et al., *Am. J. Hematol.*, **9**:13, 1980), hepatoma (Giannoulis, *Digestion*, **30**:236, 1984) and recently Hodgkin's disease (Bezвода et al., *Scand. J. Haematol.*, **35**:505, 1985). In assays based on antibodies HeLa cell ferritin, Hazard and Drysdale found higher concentrations of ferritin in sera from patients with various tumors than in the same sera assayed by antibodies directed against normal liver ferritin (Hazard et al., *supra*). Others have failed to demonstrate a consistent pattern of iso-ferritins in tumor tissues (Cragg et al., *Br. J. Cancer*, **35**:635, 1977; Halliday et al., *Cancer Res.*, **36**:4486, 1976) or in sera obtained from patients with tumors (Jones et al., *Clin. Chim. Acta.*, **85**:81, 1978; Jones et al., *Clin. Chim. Acta.*, **106**:203, 1980).--

Please replace the paragraph beginning at the bottom of page 3, with the following rewritten paragraph:

D³ --Breast cancer is a malignant disease effecting different populations at a rate of one to every 9-13 of women. Early diagnosis of breast cancer is known to considerably improve the prognosis of the patient. Diagnosis of breast cancer is based today mainly on imaging techniques such as mammograms verified at times by biopsies. Blood-based assays of breast cancer have been reported in the literature, for example, biomarkers such as CA 15.3 (Daly, L. et al., *Comparison of a novel assay for breast cancer mucin to and CA 54 15.3 carcinoembryonic antigen*, *J. Clin. Oncol.*, **10**:1057-65, 1992); the CA 549(2) marker (Dormers, I. J., et al., CA 549; a new tumor marker for patients with advanced breast cancer *J. Clin. Lab. Anal.*, **2**:168-73, 1988); and the marker CA M29 CEA (Duistrian, A. M. et al., *Evaluation of CA M26, CA M29, CA 15.3 and CEA as circulating tumor markers in breast cancer patients*. *Tumor Biol.*, **12**:82-90, 1991). However these assays,

D³ reported in the scientific community have not gained, to date, clinical significance (Werner M., et al., *Clinical utility and validation of emerging biochemical markers from mammary adenocarcinoma*, *Clin. Chem.*, **39/11**(B):2386-96, 1993).--
